## REMARKS

Claim 25 has been amended to incorporate the limitations of former claim 35 and retains the limitation that the agents associated with delivery vehicles are antineoplastic. Limitation to maintaining the ratio for one hour is found at least in Example 5 as shown in Figure 8, and Example 8 as shown in Figure 12. Support for the types of delivery vehicles set forth in claim 25 is found in claim 10 as originally filed in the PCT application.

Thus, claim 25 contains no new matter. Claims 41 and 51 have been correspondingly amended. Claims 32-38, 43-44 and 47-50 have been canceled. New claims 54-56 which depend ultimately from claim 41 are based on former claims 30, 39 and 40. Entry of the amendment is respectfully requested.

Double-Patenting

A terminal disclaimer is provided with respect to Serial No. 10/417,631, now U.S. patent 7,850,990. Also provided are terminal disclaimers with respect to applications Serial No. 11/701,326, Serial No. 11/304,328 and Serial No. 11/841,786.

The filing of these terminal disclaimers obviates the double-patenting rejections of record.

The Rejection Under 35 U.S.C. § 112, Paragraph 1

The Examiner objects to the claim scope based on the infamous *Wands* factors. The nature of the invention is accurately stated, although the claims are limited to antineoplastic agents. Applicants appreciate that the Examiner acknowledges that the state of the prior art is high in terms of formulating liposomal or other particulate sustained release compositions, but disagree that the skilled artisan is not able to design vehicles that maintain an administered ratio *in vivo*. The parameters that affect rates of drug release from various particulate delivery vehicles is quite well

advanced. There is extensive literature with respect to a variety of drug formulations including those set forth in claim 25. Enclosed herewith is a Declaration of Dr. Lawrence Mayer with respect to liposomes in particular.

Applicants also appreciate the acknowledgement that the ordinary skill in the art is very high.

Applicants acknowledge that antineoplastic agents or agents in general can be either positively charged or negatively charged or neutral and that the release rate will depend on the nature of the agent and its interactions with the delivery vehicle components. Applicants also acknowledge that some of the agents are lipophilic. Thus, it may not be possible to associate both of the agents with the same delivery vehicle. However, as is made clear by the claims as originally filed, the agents need not be associated with the same delivery vehicle. Because sustained release particulate formulations have been the object of study for many decades, the behavior of individual agents with respect to any particular delivery system, as the Examiner acknowledges, is well advanced. Since the agents need not be encapsulated in the same particle, the knowledge considering individual behavior with respect to said particles is relevant. Thus, the basis for the determination of unpredictability is not consistent with the possibilities included in the invention and the Examiner's recognition of the state in this art..

Applicants acknowledge that the claims are broad in the sense that a variety of agents can be considered to be within the scope of the claims and the delivery vehicles are of various types. However, all that is required is to maintain a predetermined non-antagonistic ratio of this variety of agents and with the variety of particulates available, this is well within the skill of the art. The guidance provided with respect to determination of the non-antagonistic ratio is quite extensive.

The specification describes in detail the well known method of Chou-Talalay which is even commercially available to determine non-antagonistic ratios of drugs.

The application does have working examples, confirming that the invention can readily be practiced.

As to the quantity of experimentation necessary, as noted, there is a commercially available method for determining a non-antagonistic ratio, so that what that ratio is can readily be determined. Further, as the Examiner kindly acknowledges, the behavior of individual agents *vis-à-vis* particulate delivery systems is well advanced, and since each agent can be associated with a different particle, this knowledge can be applied to coordinate the pharmacokinetics. Again, it should be noted that it is not necessary to coencapsulate or coassociate the agents with the same particulate delivery vehicles. Separate delivery vehicles with coordinated pharmacokinetics with respect to perhaps differing drugs may be employed.

Based on the foregoing, the rejection for lack of enablement may be withdrawn.

The Rejection Under 35 U.S.C. § 112, Paragraph 2

The first basis for rejection that is it unclear as to what applicants convey by "non-antagonistic ratio". The specification extensively discusses what is meant, and it is believed that the claims as amended make this clear. Claim 25 defines a non-antagonistic ratio as that determined in an *in vitro* assay where the agents have a non-antagonistic biological effect over at least 20% of the concentration range over which the fraction of cells affected is 0.2-0.8. What the biological effect is, and what cells should be used in the assay are clarified, for example, in paragraphs 97 and 98 which explain that the cells relevant to the agents are those that will respond to the effects of these

agents and the nature of the biological effect will, of course, depend on these cells and the nature of the agent. Such correlations are well known.

The objection to "checkpoint inhibitor" is now moot. Claim 51 is amended as suggested.

The Anticipation Rejection

Claims 25-28 and 30-38 were rejected as assertedly anticipated by Saxon (*J. Liposome Res.* (1999)). This basis for rejection is in error as Saxon does not describe a composition comprising particulate delivery vehicles with first and second agents that maintain the administered ratio for at least an hour. As set forth on page 515, when vincristine and mitoxantrone were administered simultaneously in liposomes, within one hour, 90% of vincristine was lost, but only 30% of the mitoxantrone was lost. Thus, the ratio was drastically altered in the plasma rather than maintained. Accordingly, Saxon does not anticipate the claimed composition of claims 25-28 or 30-31. Claims 32-38 have been canceled.

The Obviousness Rejections

All claims were rejected as obvious over Saxon. This rejection may be withdrawn for the same reason as set forth previously. Far from anticipating or suggesting the invention, Saxon teaches away by describing compositions where the ratio of two administered agents is rapidly altered after administration.

Claims 25-53 were rejected as assertedly obvious over the combination of Engblom (*Brit. J. Cancer* (1999)) or Kano (*Leukemia Res.* (1993)) or Guichard (*Biochem. Pharmacol.* (1998)) or WO01/10416 ("WO01") in combination with asserted admissions of applicants and in further combination with Fountain (5,000,958).

WO01 is clearly inapposite as it merely states the acknowledged prior art that many treatments, especially for cancer, are combination treatments and that sustained release formulations can be used. It is the purpose of the invention to improve such compositions by maintaining non-antagonistic ratios after administration. The citations of Engblom, Kano and Guichard merely illustrate the ease with which non-antagonistic ratios may be determined *in vitro*, but they miss the point of the invention which is to maintain these ratios after administration. Neither they nor WO01 suggest or allude to this. The asserted admissions by applicants are only consistent with the ease with which non-antagonistic ratios can be determined *in vitro*. Therefore, Fountain is cited as teaching that one can encapsulate two drugs in liposomes after determining their non-antagonistic action *in vitro*, but Fountain does not remedy the foregoing defect. There is nothing in Fountain that describes the ratio as being maintained once administration is accomplished. Fountain never discusses maintaining an administered ratio, and Fountain, of course, does not anticipate inherently since the agents in claim 25 are not antimicrobial agents.

Claims 25-53 were rejected as assertedly obvious over Engblom, Kano, Guichard or WO01 in combination with applicants' statement of prior art and in further combination with Vaage (*Int. J. Cancer* (1993)), Saxon, and Bally (5,736,155) individually or in combination and optionally in further combination with Fountain.

Engblom, Kano, Guichard and WO01 have been discussed above as have Saxon and Fountain. As noted, the object of the invention is to maintain an administered ratio (which is non-antagonistic) of agents in the blood for at least one hour after administration. Fountain is silent on this issue and Saxon appears to teach away from it by illustrating compositions where the ratio is drastically altered after administration. Vaage also teaches away from the central concept of the

invention as shown in Figure 5 where simultaneous administration of Doxil® and S-VCR, shown as bar 6, is less effective than Doxil® alone, shown as bar 3. The only effective non-antagonistic coadministrations of S-VCR and Doxil® are on alternating schedules, which teaches away from using a single composition as required by the claims. That is, if a non-antagonistic ratio were included in the liposomes of bar 6 in Figure 5 to begin with, the ratio must have been drastically altered after administration.

This leaves Bally which shows coencapsulation of antineoplastic agents, but employs liposomes that are inherently unstable and incapable of maintaining any ratio of these agents.

One of the documents from which priority is claimed, U.S. provisional application 60/341,529 filed 17 December 2001, in working Example 3, prepares liposomes with combinations in the ratios disclosed in Bally and demonstrates that they fail to meet the limitation currently in claim 25, namely that a non-antagonistic effect is exhibited over at least 20% of the concentration range such that the fraction of the cells are affected in an *in vitro* assay is 0.20-0.80. The protocol of said Example 3 and the corresponding figure showing results are enclosed.

The formulation of Bally as described in Part C in column 15 thereof also teaches away from the invention because the liposomes used are incapable of stable association with any drugs at all. The compositions of Bally are LUVs composed entirely of egg phosphatidylcholine (see line 39) and egg phosphatidylcholine vesicles are inherently incapable of stable association with drugs *in vivo*. This is verified by the enclosed publication of Scherphof, G., *et al.*, *Biochim et Biophys Acta* (1978) 542:296-307, entitled "Disintegration of Phosphatidylcholine Liposomes in Plasma as a Result of Interaction with High-Density Lipoproteins." In the summary, it is stated that "massive release of entrapped labeled albumin from the liposome during incubation with plasma

suggests that the observed release of phosphatidylcholine from the liposomes has a highly destructive influence on liposomal structure." There is no suggestion in Bally that any ratio be maintained *in vivo*.

Again, applicants emphasize that it is not enough that the secondary documents suggest that some drugs be put into liposomes, the invention requires more than that. It requires that a non-antagonistic ratio be placed in liposomes in such a way that that ratio is maintained when administered. And the documents cited to teach the invention when combined with Engblom, Kano, Guichard or WO01 and Fountain, actually teach away from it. Accordingly, this basis for rejection may be withdrawn.

Claims 25-53 were rejected as assertedly unpatentable over the same documents set forth above and in further view of Giles (US2003/0083316). Giles is cited simply as disclosing the algorithm which applicants have already acknowledged is in the art. Giles does not remedy the deficiencies of the remaining documents which fail to show any compositions that are designed to maintain the administered ratio of two agents for at least one hour after administration. Accordingly, this basis for rejection may also be withdrawn.

Conclusion

The invention lies in administering a non-antagonistic ratio of antineoplastic agents and to maintain that non-antagonistic ratio for at least one hour after administration.

The Examiner has kindly acknowledged that the skill in the art is high in regard to designing systems for single agents in particulate delivery vehicles, and since separate delivery vehicles can be used for the agents administered in the composition, this clearly permits appropriate design of coordinated pharmacokinetics for the two agents in order to maintain the administered ratio, even if

they cannot be accommodated in the same particle. Thus, the rejection for lack of enablement may be withdrawn.

There is no document in the art that describes particulate delivery vehicles with non-antagonistic combinations of agents that are designed to maintain an administered ratio of these agents. In fact, three of the cited documents, Saxon, Bally and Vaage, specifically describe compositions of particulate vehicles containing combinations of drugs where the ratio is not maintained.

Thus, claims 25-31, 39-41, 44-46 and 51-56 are in a position for allowance and passage of these claims to issue is respectfully requested.

Should minor issues remain that could be resolved over the phone, a telephone call to the undersigned is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 532552000102.

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Respectfully submitted,

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